639. *A Search for New Trypanocides. Part II.** 4-*Amino*-6-*dialkylaminoquinaldines.*

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Some 6-*NN*-disubstituted derivatives of 4 : 6-diaminoquinaldine are described, of which only 4-amino-6-piperidinoquinaldine had a curative effect on *Trypanosoma rhodesiense* infections in mice.

The 4 : 6-diaminoquinaldine structure occurs in several chemotherapeutic drugs, such as Surfen-C, Antrycide, αω-di-(4-amino-6-quinaldyl)aminoalkanes,[1] and diamides derived from 4 : 6-diaminoquinaldine and various dicarboxylic acids.[2] Having discovered [3] that 4-amino-6-piperidinoquinaldine possessed activity against *Trypanosoma rhodesiense*, we decided to prepare further compounds of this type, *e.g.*, 4-amino-6-dialkylaminoquinaldines.

The first attempt was by direct alkylation of 4 : 6-diaminoquinaldine with alkyl halides in presence of alkali in ethanol or aqueous ethanol. Whereas the 6-amino-group reacts as a true amino-group, the other resembles the amino-group in 4-aminopyridine and behaves as in the tautomeric 4-quinolone imide. In view of this, dialkylation of the 6-amino-group was attempted, although it was realised that some of the 1-alkyl-4-quinolone imide might also be formed. These alkylations were unsuccessful, but in one case a small yield of 4-amino-6-diethylaminoquinaldine ethiodide was obtained.

A possible alternative route seemed to lie in the reaction between the lithium derivatives of dialkylamines with 4-amino-6-bromoquinaldine, a reaction which is successful with aromatic bromides.[4] However, reaction of 4-amino-6-bromoquinaldine (prepared by fusing 6-bromo-4-methoxyquinaldine with ammonium acetate) with lithium diethylamide in ether gave only tars. The required dialkylamino-derivatives were finally obtained from the corresponding *p*-dialkylaminoanilines by the Conrad–Limpach reaction, and conversion of the resulting 6-dialkylamino-4-hydroxyquinaldines successively into the 4-chloro- and 4-amino-analogues.

4-Amino-6-pyrrolidino- and 4-amino-6-piperidino-quinaldine were prepared by direct reaction of the appropriate polymethylene dibromide with 4 : 6-diaminoquinaldine in ethanol at 160—180°.

All the compounds formed colourless dihydrochlorides, but often (mainly with the 4-chloro-intermediates) the salts tended to lose hydrogen chloride on exposure to air or when heated.

None of these compounds was active against *T. congolense* infections in mice, and only 4-amino-6-piperidinoquinaldine had a curative effect on *T. rhodesiense* infections.

Experimental

N-*Methyl*-N-n-*propylaniline*.—Recorded preparations [5] were improved as follows. *N*-Methylaniline (80 g.) was heated with *n*-propyl bromide (110 g.) at 95° for 22 hr. Treating the cold, solidified mixture with excess of 50% aqueous sodium hydroxide gave an oil, which after isolation by means of ether, yielded *N*-methyl-*N*-*n*-propylaniline (99 g.), b. p. 116·5—119°/12 mm., $n_D^{19\cdot5}$ 1·5403. The picrate crystallised from ethanol in yellow prisms, m. p. 109·5° (lit.,[6] 106—107°, 110·5°).

p-*Amino*-N-*methyl*-N-n-*propylaniline*.—The crude nitroso-derivative prepared by Stoermer and von Lepel's method [5] from *N*-methyl-*N*-*n*-propylaniline (89 g.), concentrated hydrochloric acid (116 c.c.), and sodium nitrite (46 g.), was added with stirring and cooling to a solution of crystalline stannous chloride (210 g.) in concentrated hydrochloric acid (240 c.c.). The mixture was then refluxed for 30 min. and left to cool; then the base was liberated by 50% aqueous

* Part I, *J.*, 1956, 337.

[1] Jensch, *Z. angew. Chem.*, 1937, **50**, 891; U.S.P. 2,050,971.
[2] Pratt and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 4065; Goble, *J. Pharmacol.*, 1950, **98**, 49.
[3] Stone, personal communication.
[4] Cf. Hornung and Bergstrom, *J. Amer. Chem. Soc.*, 1945, **67**, 2110; Gilman *et al.*, *ibid.*, 1945, **67**, 2106; 1946, **68**, 143.
[5] Claus and Hirzel, *Ber.*, 1886, **19**, 2787; Stoermer and von Lepel, *Ber.*, 1896, **29**, 2112.
[6] Singh, *J.*, 1916, **109**, 791; Wagner, *J. Amer. Chem. Soc.*, 1933, **55**, 724.

sodium hydroxide; distillation gave p-*amino*-N-*methyl*-N-n-*propylaniline* (66 g.), b. p. 154—155°/17 mm., $n_D^{23\cdot5}$ 1·5670 (Found: N, 16·9. $C_{10}H_{16}N_2$ requires N, 17·05%).

NN-*Di*-n-*butylaniline*.—Conditions, mentioned by Reilly and Hickinbottom,[7] were supplemented as follows: aniline (36·1 c.c., 0·4 mol.) and *n*-butyl bromide (43·2 c.c., 0·4 mol.) were refluxed for 40 min. The oil obtained on addition of aqueous sodium hydroxide gave mono-*n*-butylaniline (36·5 g.), b. p. 253—259°/760 mm., n_D^{22} 1·526. This amine (121 g., 0·8 mol.) and *n*-butyl bromide (130 c.c., 1·2 mol.) were refluxed, in presence of a trace of iodine, for 24 hr. Basification of the reaction mixture afforded di-*n*-butylaniline (126 g.), b. p. 270—275°/760 mm., n_D^{20} 1·5195—1·5200.

p-*Amino*-NN-*di*-n-*butylaniline*.—The above tertiary amine (116·6 g.) was converted into *NN*-di-*n*-butyl-*p*-nitrosoaniline hydrochloride (137 g.), m. p. 105—106°, as described by Reilly and Hickinbottom,[7] by using water (550 c.c.), concentrated hydrochloric acid (290 c.c.), and sodium nitrite (39·4 g.). The nitroso-derivative was reduced to the amine, as described above, with stannous chloride (300 g.) in concentrated hydrochloric acid (360 c.c.). The white suspension was not heated, but was stirred at room temperature for 1 hr. Basification and extraction with benzene gave *p*-amino-*NN*-di-*n*-butylaniline (72 g.), b. p. 127—128°/0·15 mm., n_D^{22} 1·5378—1·5382, which quickly darkened in air. The *dihydrochloride* crystallised from ethanol in colourless prisms, m. p. 206—207° (Found: C, 55·6; H, 9·4; N, 9·25. $C_{14}H_{24}N_2$,2HCl,0·5H_2O requires C, 55·6; H, 9·0; N, 9·25%).

4-*Amino*-6-*piperidinoquinaldine Dihydrochloride*.—4 : 6-Diaminoquinaldine (10·5 g.), 1 : 5-dibromopentane (6 g.), and ethanol (40 c.c.) were heated at 150° for 3 hr. The mixture was filtered, and the filtrate was evaporated *in vacuo*, to give a yellow solid. Treating this with dilute sodium hydroxide gave the oily base, which after being washed with water by decantation, was treated with methanolic hydrochloric acid. This gave a solid (17·3 g.), which crystallised from ethanolic hydrochloric acid as the *dihydrochloride* (9·45 g.), yellow prisms, sinter from 245°, char from 297° (Found: C, 56·7; H, 6·85; N, 13·15; Cl, 22·3. $C_{15}H_{19}N_3$,2HCl requires C, 57·3; H, 6·75; N, 13·35; Cl, 22·55%).

4-*Amino*-6-*pyrrolidinoquinaldine Dihydrochloride*.—This was prepared similarly from 4 : 6-diaminoquinaldine (10·35 g.), 1 : 4-dibromobutane (6 g.), and ethanol (30 c.c.). The *dihydrochloride* (15·1 g.) crystallised from ethanol in pale yellow prisms, m. p. 215° (decomp.) (Found: C, 52·35; H, 6·95; N, 13·8; Cl, 22·0. $C_{14}H_{17}N_3$,2HCl,H_2O requires C, 52·85; H, 6·65; N, 13·2; Cl, 22·25%).

6-*Bromo*-4-*methoxyquinaldine*.—6-Bromo-4-hydroxyquinaldine[8] (100 g.), methyl sulphate (72·4 c.c.), and dry toluene (480 c.c.) were refluxed and stirred for 2 hr. The resulting brown solid was filtered off and washed with ether; it was dissolved in hot water (200 c.c.), the solution was filtered, and excess of 50% aqueous sodium hydroxide was added to the hot filtrate. The oil solidified and the solid was washed with water and extracted several times with boiling light petroleum (b. p. 40—60°; 7 l.). The extract gave 6-bromo-4-methoxyquinaldine (85 g.) which crystallised from light petroleum (b. p. 40—60°) in pinkish needles, m. p. 90—92° (Found: N, 5·7; Br, 32·2. $C_{11}H_{10}ONBr$ requires N, 5·5; Br, 31·75%). This compound was first prepared by Mr. S. S. Berg.

4-*Amino*-6-*bromoquinaldine*.—6-Bromo-4-methoxyquinaldine (20 g.) and ammonium acetate (85 g.) were heated with stirring at 135—140° for 10 min.; a clear orange melt was obtained. After further heating for 3 hr. the melt was poured into water (250 c.c.), whence basification with 50% aqueous sodium hydroxide gave 4-*amino*-6-*bromoquinaldine* (16·6 g.), m. p. 167—169° colourless prisms (from water), m. p. 173° (Found: N, 11·6; Br, 33·6. $C_{10}H_9N_2Br$ requires N, 11·8; Br, 33·75%).

6-*Dimethylamino*-4-*hydroxyquinaldine*.—*p*-Dimethylaminoaniline (77 g.), ethyl acetoacetate (67 g.), and concentrated hydrochloric acid (4 drops) were mixed. Reaction soon occurred with elimination of water, and after 2 hr. the resulting solid was powdered and dried *in vacuo*, giving crude *ethyl* 2-(p-*dimethylaminoanilino*)*crotonate* (135 g.), which recrystallised from light petroleum (b. p. 40—60°) (charcoal) as pale orange, prismatic needles, m. p. 69—70° (Found: C, 67·7; H, 8·15; N, 11·3. $C_{14}H_{20}O_2N_2$ requires C, 67·7; H, 8·1; N, 11·3%). This ester (133 g.) was added during 10 min. to boiling and stirred Dowtherm (diphenyl ether–diphenyl) (1 l.); after boiling for a further 15 min. the mixture was left overnight, then the solid (82 g.) was filtered off and washed with light petroleum (b. p. 40—60°) and ether. The 6-*dimethylamino*-4-*hydroxyquinaldine* crystallised from ethanol–ether (1 : 3) in bright yellow prisms, m. p. 320—322° (Found: C, 71·5; H, 7·1; N, 14·15. $C_{12}H_{14}ON_2$ requires C, 71·25; H, 6·95;

[7] Reilly and Hickinbottom, *J.*, 1918, **113**, 101.
[8] Kermack and Weatherhead, *J.*, 1939, 564.

N, 13·85%). The *dihydrochloride* crystallised from ethanol in colourless prisms, m. p. 264—265° (Found : Cl, 25·5. $C_{12}H_{14}ON_2$,2HCl requires Cl, 25·75%).

4-Chloro-6-dimethylaminoquinaldine.—A solution of 6-dimethylamino-4-hydroxyquinaldine (77 g.) in phosphorus oxychloride (385 c.c.) was refluxed for 30 min., and the mixture was cooled, poured on ice, and basified with 50% aqueous sodium hydroxide. The *chloro-compound* (71 g.), which was extracted by ether, crystallised from ether in bright yellow needles, m. p. 91—92° (Found : C, 65·5; H, 6·35; N, 12·9; Cl, 15·7. $C_{12}H_{13}N_2Cl$ requires C, 65·3; H, 5·95; N, 12·7; Cl, 16·05%). The *hydrochloride* formed colourless prisms, which reddened in air, and became orange when dried at 76° *in vacuo*. The latter form, m. p. 256°, was stable (Found : N, 10·4; Cl, 32·4. $2C_{12}H_{13}N_2Cl$,3HCl requires N, 10·15; Cl, 32·2%).

4-Amino-6-dimethylaminoquinaldine.—Ammonia was passed through a refluxing solution of 4-chloro-6-dimethylaminoquinaldine (15 g.) in phenol (75 g.) which was kept at 180—200° (bath-temp.) for 3 hr. Phenol was then removed by distillation with steam; basification of the residue gave a green solid (13·7 g.). Recrystallisation from ethanol (30 c.c.)–ether (175 c.c.)–light petroleum (b. p. 40—60°; 175 c.c.) gave *4-amino-6-dimethylaminoquinaldine* (12·2 g.), green prisms, which after crystallising successively from hot water and from chloroform–light petroleum (b. p. 40—60°) was obtained in pale green prisms, m. p. 201—203° (Found : N, 21·0. $C_{12}H_{15}N_3$ requires N, 20·85%). The *dihydrochloride* (6·1 g. from 5 g. of base) crystallised from ethanol–methanol (1 : 2) in colourless needles, m. p. 245—246° (Found : N, 15·5; Cl, 25·5. $C_{12}H_{15}N_3$,2HCl requires N, 15·35; Cl, 25·8%).

Ethyl β-(p-*diethylamino-* (80%), straw-coloured prisms (from light petroleum), m. p. 65—66° (Found : N, 10·2. $C_{16}H_{24}O_2N_2$ requires N, 10·15%), and *ethyl* β-(*p-N-methyl-N-propylamino-anilino*)*crotonate* (95%), colourless prisms (from light petroleum), m. p. 58·5° (Found : C, 69·45; H, 8·7; N, 10·2. $C_{16}H_{24}O_2N_2$ requires C, 69·55; H, 8·75; N, 10·15%), were similarly prepared. The oily di-*n*-butylamino-analogue was cyclised without purification.

Other *compounds*, prepared by cyclisation as above, are recorded in the Table.

4-Substituted 6-dialkylaminoquinaldines.

No.	4-Subst.	*N*-Subst		Deriv [a]	Yield (%)	M. p.	Solvent [b] for crystn.	Cryst. form
1	OH	Et	Et	—	62	198—199°	EtOH–Et_2O	Needles
				Salt		238	EtOH–HCl	Prisms
2	OH	Me	Pr^n	—	74	186	EtOH–Et_2O	Green prisms
				Salt		208—209	EtOH	Pale yellow prisms
3	OH	Bu^n	Bu^n	—	—	130	C_6H_6–Et_2O	Green prisms
				Salt [c]	95	206		
4	Cl	Et	Et	—	87	34	MeOH–H_2O	Yellow needles
				Salt		216 [d]	EtOH	Straw-coloured needles
5	Cl	Me	Pr^n	—	93	56—57	Petrol	Yellow plates
				Salt		218 [d]	EtOH	Pale yellow prisms
6	Cl	Bu^n	Bu^n	Salt	40	179 [d]	EtOH–HCl	Needles
7	NH_2	Et	Et	—	95	170·5	$CHCl_3$–Petrol	Pale green needles
				Salt	—	222—223	EtOH	Plates
8	NH_2	Me	Pr^n	Salt	63	197—198	EtOH	Prisms
9	NH_2	Bu^n	Bu^n	Salt	50	203—204	EtOH–HCl	Pale yellow plates

		Found (%)					Required (%)			
No.		C	H	N	Cl	Formula	C	H	N	Cl
1	Base	72·8	7·65	11·9	—	$C_{14}H_{18}ON_2$	73·0	7·9	12·15	—
	Salt				23·2					23·4
2	Base	72·4	7·95	12·1	—	,,	,,	,,	,,	—
	Salt			9·35					9·2	
3	Base	75·0	9·3	9·9	—	$C_{18}H_{26}ON_2$	75·5	9·15	9·8	—
	Salt			8·1					7·8	
4	Base	—	—	11·1	13·95	$C_{14}H_{17}N_2Cl$	—	—	11·3	14·25
	Salt	52·4	6·1	8·6			52·3	5·95	8·7	—
5	Base	67·65	6·65	11·5	14·0	,,	67·6	6·9	11·3	14·25
	Salt	51·8	6·05	8·85	32·8		52·3	5·95	8·7	33·1
6	Salt	57·2	7·2	6·9	28·4	$C_{14}H_{17}N_2Cl$,2HCl	57·25	7·2	7·4	28·15
7	Base	—	—	18·3	—	$C_{14}H_{19}N_3$	—	—	18·3	—
	Salt	55·1	7·2	13·8	23·3	—	55·6	6·95	13·9	23·5
8	Salt	—	—	13·8	22·9	$C_{14}H_{19}N_3$,2HCl	—	—	13·9	23·5
9	Salt	—	—	11·4	—	$C_{18}H_{27}N_3$,2HCl	—	—	11·7	—

[a] " Salt " in this column = dihydrochloride. [b] Petrol = light petroleum (b. p. 40—60°). [c] After cyclisation of the crotonate, benzene was added to the Dowtherm which was then treated with hydrogen chloride. [d] Becomes red in air.

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